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重點一子題 4---不對稱水相羥甲基化反應---開發及應用(I)
Asymmetric Hydroxymethylation in Aqueous Media---Development and Application (I)

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中文摘要

帶有手性中心的丁烯醇(1)是有機合成上重要的合成單體，其傳統合成方法是由帶有手性中心的 3-羥基 2-甲基丙酸甲酯經多步驟合成而來。本研究計畫提出新合成策略，發展不對稱水相羥甲基化反應，以此不對稱合成技術能精簡合成步驟，更有效合成帶有手性中心的丁烯醇。甲醛在有機合成上為優質單碳來源，但因甲醛單體易聚合且不易製備，使甲醛在有機合成上的應用受到極大限制。而傳統不對稱烯丙基化反應，其反應產物所產生新的手性中心，是取決於醛的反應位向。我們發展不對稱水相羥甲基化反應，是使用市售甲醛水溶液為反應試劑，進行烯丙基化反應，而反應產物丁烯醇(1)產生新的手性中心，是取決於烯丙基的反應位向。此為新穎不對稱合成技術。發展不對稱水相羥甲基化反應，是使用甲醛水溶液為反應試劑，除進行烯丙基化反應，我們也發展苯甲基化反應，可應用在合成帶有手性中心的苯丙酸。帶有手性中心的苯丙酸像 Naproxen, Ibuprofen 為非類固醇性抗炎藥，用於治骨關節炎和類風濕性關節炎。

關鍵字：不對稱合成

Abstract

Chiral functionalized homoallylic alcohol 1 is a useful building block in organic synthesis. Isoprene is a C5 unit found in many natural products, and the synthetic application of homoallylic alcohol 1 is reported in the synthesis of terpenoid hydrocarbons, macrolides and polyether antibiotics. The general synthetic route to access homoallyl alcohol 1 is from methyl (R)-3-hydroxy-2-methylpropionate. Herein, a novel aqueous asymmetric hydroxymethylation of γ-substituted allyl halides was proposed. The preparation of homoallylic alcohols could be performed by the addition of an organometallic reagent with formaldehyde. Although formaldehyde is a good source for one-carbon homologation, the intrinsic polymerization of formaldehyde monomer limited the scope of Lewis acid catalyzed allylation of formaldehyde. The C-C bond formation is not feasible with volatile and unstable aldehydes in the classical method of Lewis acid catalyzed allylation reactions. As the source of formaldehyde, the use of a commercial formaldehyde aqueous solution is the most convenient. The metal-mediated Barbier-type allylation of formaldehyde would provide a facile route to homoallylic alcohols. The development of asymmetric hydroxymethylation of γ-substituted allyl halides in aqueous media was stated in this proposal. In addition, the metal-mediated hydroxymethylation of 1-haloethyl-benzene was proposed. The application of this novel aqueous asymmetric hydroxymethylation of 1-haloethyl-benzene is a new route to the synthesis of ibuprofen and naproxen.

Key words：Asymmetric catalysis; Aqueous solution; Hydroxymethylation